Genetic influences on treatment-seeking for common mental health problems in the UK Biobank

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Abstract

The majority of those who experience clinical anxiety and depressive symptoms do not receive treatment. Studies investigating inequalities in treatment outcomes rarely consider that individuals respond differently to their experience of the environment. Indeed, individuals actively select their experiences. Therefore, much of our environment is under genetic influence, via our behaviour. If genes influence who seeks and receives treatment, selection bias will confound genomic studies of treatment response. Furthermore, if some individuals are at high genetic risk of seeking but not commencing treatment, then greater efforts could be made to engage them. We explored the role of genetic influences on four lifetime treatment-seeking behaviours (*treatment-seeking, treatment-receipt, self-help, self-medication*) in participants of the UK Biobank (sample size range: 48,106 - 75,322). We found that treatment-related behaviours were modestly heritable in these data. Nonetheless, we observed interesting genetic overlap between lifetime treatment related-phenotypes and psychiatric disorders, symptoms and behavioural traits.

Introduction

One in six adults experience clinical anxiety and/or depressive symptoms in any given week in the UK, but only one in three of those in need of treatment report currently using a treatment (McManus et al. 2016). The disparity between the number of individuals with clinical symptoms and those that receive treatment is called the treatment gap (Kohn et al. 2004). A number of studies have estimated that as many as 75% of individuals who have a 12 month diagnosis of depression do not receive treatment (Chisholm et al. 2016; Thornicroft 2008; Thornicroft et al. 2017). This is despite many such individuals acknowledging a need for treatment and having contacted services. Some evidence for demographic inequalities in who receives treatment exists. Within the UK, individuals who are White British, female, or middle-aged were more likely to receive treatment than those who were not (McManus et al. 2016). Individuals from lower socioeconomic backgrounds are more likely to have sought but not actually received treatment (McManus et al. 2016; Delgadillo et al. 2016). There are many reasons why individuals might not seek treatment, such as a lack of knowledge to identify clinical symptoms (i.e. poor mental-health literacy), lack of awareness about treatment options, negative beliefs about the effectiveness of treatment, and stigma (i.e., perceived prejudice and/or discrimination against people diagnosed with mental health conditions; (Henderson, Evans-Lacko, and Thornicroft 2013).

Twin studies have shown that a proportion of the variation in nearly all complex human traits can be explained by genetic variation (on average ~50%; Polderman et al. 2015). This is known as heritability, the proportion of variation in an observable trait attributed to genetic factors, in a given population at a particular time-point (Visscher, Hill, and Wray 2008). Analysis of genome-wide genetic data in many traits has shown that a proportion of heritability can be explained by the additive effects of common genetic variants (genetic variation in 1% of the genome, that occurs in >1% of the population). Variation in disorders (e.g. Anxiety and Major Depressive Disorder), personality traits, (e.g. neuroticism, openness, conscientiousness), and life outcomes (e.g. educational attainment) can be explained by common genetic variation (common genetic variant heritability; h^2_{SNP} range: 5-30%; Brainstorm Consortium et al. 2018).

Studies investigating causes of treatment inequalities do not always account for the fact that individuals differ in their response to the environment (Spinath and Bleidorn 2017). Whether an individual

receives treatment, and the type of treatment they receive, are components of their environment. Many environmental influences have been found to be heritable (Kendler and Baker 2007). Environments known to be heritable include experience of stressful life events, social support and marital quality (Kendler and Baker 2007). Of particular note, the genetic influences on such environmental experiences (e.g. stressful life events or social deprivation) overlap considerably with those on traits of interest such as depression (Thapar, Harold, and McGuffin 1998; Hill et al. 2016). This indicates that genetic variation influences correlations between behaviour and life experiences. In other words, genetic factors influence behaviour, which plays a major role in shaping our environment, so called gene-environment correlation.

One approach to understanding how genetic influences on different traits relate to one another is to examine their genetic correlation. Exploring genetic correlations allows us to garner information about where genetic influences on the trait of interest (e.g. treatment seeking) come from. Shared genetic variation can indicate that specific genetic variants influence the two traits independently. Alternatively, in the case where trait A directly influences trait B, any genetic effects on trait A will also influence trait B (Gage et al. 2016). For example, genetic effects might impact on both anxiety symptoms and treatment seeking. Genes influencing greater symptom severity are likely to influence need for treatment. Different genes influencing personality traits, for example openness, might also lead an individual to be more open about their experiences, in turn promoting treatment-seeking. Indeed, the decision to seek and then commence treatment, may depend in part on genetically influenced individual characteristics, which themselves impact on treatment-seeking behaviours.

Whether or not genes influence treatment-seeking should also be of particular interest to researchers investigating genetic influences on treatment response. It will be important to identify genetic influences on treatment-seeking and control for them in genomic studies of treatment response. It is also important to consider that only those who seek treatment will receive it, which may have implications for studies and trials investigating treatment efficacy. Those who do not seek treatment (or who seek but do not receive treatment) will be excluded from such analyses, which could bias estimated effects of treatment. For example, belief in the positive effects of treatment has been linked with adherence to treatment and favourable response (Ownby et al. 2014; J. Carter et al. 2006; J. D. Carter et al. 2015;

Lambert and Barley 2001). Whereas, negative beliefs about treatment have been associated with reluctance to seek help (Henderson, Evans-Lacko, and Thornicroft 2013). By not including individuals with negative beliefs about treatment efficacy, the positive effects of treatment might be overestimated. Furthermore, if individuals who need treatment are at high genetic risk of not taking up treatment, then greater efforts could be made to engage them and improve compliance with treatment.

We explored the role of genetic influences on lifetime treatment-seeking behaviours in a large UK population study, the UK Biobank. We defined four treatment-related phenotypes in response to symptoms of anxiety or depression; **treatment-seeking** (*have you ever from sought help from a professional?*), **treatment-receipt** (*have you ever received talking therapy or prescription medication?*), **self-help** (*have you ever used a structured therapeutic activity or over the counter medications to alleviate symptoms?*), and **self-medication** (*have you ever used drugs or alcohol to alleviate symptoms?*). We estimated the common variant heritability of these phenotypes and examined genetic correlations with psychiatric disorders and behavioural traits. We aimed to determine whether treatment-related phenotypes have genetic influences distinct from those influencing symptoms. Therefore, where possible we stratified our analyses based on whether individuals meet diagnostic criteria for an anxiety or depressive disorder diagnosis. Here, we specifically examined whether there were genetic influences on reluctance to seek treatment in those who need it ('cases') and on seeking treatment despite not meeting diagnostic criteria ('controls').

Methods

Sample & Phenotypes

The UK Biobank is a UK population study of approximately half a million individuals aged between 40 and 70 (Allen et al. 2014). The study originally assessed a range of health-related phenotypes and biological measures including genome-wide genotype. More recently a follow-up, online mental health questionnaire was completed by 157,366 participants (Davis et al. 2018). The mental health questionnaire assesses common mental health conditions, including lifetime symptoms of anxiety

and depression, and experiences of healthcare. Specifically, participants who reported having worried for a period of six months or longer, having worried more than most people would in a similar situation, having prolonged loss of interest in normal activities, or prolonged feelings of sadness or depression they were asked: *"Did you ever tell a professional about these problems (medical doctor, psychologist, social worker, counsellor, nurse, clergy, or other helping professional)?*".

From these data, we defined four treatment related phenotypes (see supplemental material for sample selection and phenotype definition workflow). **Treatment-seeking** participants reported on seeking help from a professional. **Treatment-receipt** was defined from participants who reported on seeking help and then receiving either prescribed medication or talking therapy for their symptoms. **Self-help** participants reported engaging in a structured therapeutic activity (e.g. mindfulness or yoga) or using over-the-counter medications to help with their symptoms. **Self-medication** was defined from those who reported using alcohol or illicit drugs in response to their symptoms.

For stratified analyses, cases were defined as those who reported sufficient severity and impact of symptoms to meet lifetime criteria for likely DSM-IV for either generalised anxiety disorder or major depressive disorder diagnoses. The **self-report items** were based on questions derived from the Composite International Diagnostic Interview (CIDI; i.e., probable lifetime diagnosis; as described in (Purves et al. 2017; Coleman et al. 2018). Cases were excluded if they self-report lifetime diagnoses of schizophrenia, other psychoses or bipolar disorder. Controls were defined as those not meeting criteria for either anxiety, or depression diagnoses, and were excluded if they reported a diagnosis of any psychiatric disorder. Individuals were excluded from analyses if they did not complete mental health online questionnaire (n=157,366), or if they did not endorse at least one of the four core common mental health screening items (worried for a period of more than six-months, worry more than most people in a particular situation, loss of interest in usual activities, prolonged feelings of sadness; Max n=75,322). It should be noted that our 'controls' endorse at least one of the four core common mental health screening items (worried for a period of more than six-months, worry more than most people in a particular situation, loss of interest in usual activities, prolonged feelings of sadness), and as such are not symptom-free. This

is a necessary condition for respondents to report on treatment-seeking in the mental health questionnaire.

The whole UK Biobank sample (N=502,616) were also asked the question: *"Have you ever seen a GP / psychiatrist for nerves, anxiety, tension or depression?".* From this data, we defined a **formal** treatment-seeking phenotype, i.e. participants who reported on seeking help specifically from their doctor or a psychiatrist. Data were available for 391,213 participants reporting on **formal** treatment seeking. For these participants, information on symptoms and diagnoses was not available. However, we saw this as an opportunity to test the reproducibility of our primary treatment-seeking analyses in a much larger sample. Results from these analyses are presented in the supplementary material.

Genetic data

Genetic data were drawn from the full release of the UK Biobank data (n=487,410; Bycroft et al. 2017). Standard quality control described previously (Coleman et al. 2018) and presented in full in the supplement were applied to the full data. Analyses were limited to common genetic variants imputed to the Haplotype Reference Consortium reference panel with high confidence (McCarthy et al. 2016). Participants were excluded if they had unusual levels of missingness or heterozygosity, they were related to another individual in the dataset, or their phenotypic and genotypic gender information was discordant. All analyses were limited to individuals of White Western European ancestry. This is because 95% of respondents to the mental health questionnaire are of White Western European ancestry. Therefore, we did not have sample sizes required to perform informative genomic analyses in other ancestry groups.

Analyses

All genomic analyses were performed on the residuals from the regression of the binary treatment related phenotypes and age, sex, six population principal components, batch and assessment centre. Analyses were performed in the whole sample and then stratified by lifetime diagnosis, and also by sex. We performed genome-wide association analyses to estimate the effects of 9.94 million genome-wide genetic variants on each phenotype (BGENIE v1.2; Bycroft et al. 2017). We then estimated how much phenotypic variance could be explained by common genome-wide genetic variants, using linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al. 2015), converting to the liability scale at the

full range of population prevalence estimates (Bulik-Sullivan et al. 2015). We tested differences between heritabilities using a block-jackknife approach (supplementary methods).

We also estimated genetic correlations (r_g) between treatment related phenotypes and also with a range of psychiatric disorders, personality and behavioural traits. We selected a range of well-powered GWAS of psychiatric, behavioural and related traits to provide a thorough examination of the genetic overlap between treatment related phenotypes and behaviour, psychopathology (for the full list, including references see supplement and/or Figure 2). Significance was assessed after Bonferroni multiple testing correction.

Results

Phenotype distribution

Phenotype and genotype data were available for participants reporting on treatment-seeking *(n=71,416)*, treatment-receipt (*n=48,106)*, self-help (*n=75,322)*, and self-medication (*n=75,128; Table 1)*. Based on the self-report items, the lifetime prevalence of generalised anxiety disorder and major depressive disorder was 11% and 38% respectively (in individuals seeking treatment). Combined, the prevalence of experiencing a common mental disorder across the lifespan was 41%. All participants in our primary sample reported experiencing at least one core symptom of anxiety or depression across their lifetime. The majority (67%) of the sample reported informing a professional about their symptoms and most of these individuals (84%) reported receiving treatment for their symptoms (i.e. 56% of the total sample). Of the whole sample, 14% report utilising some form of self-help approach such as exercise, mindfulness or over-the-counter medication, and 14% report self-medicating with alcohol or drugs.

Table 1. Treatment seeking phenotype distributions in the full sample and stratified by CIDI derived lifetime diagnosis of a common mental disorder status and sex

			Lifetime diagnosis		Sex	
		N [(a)]	***Controls*** [(b)]	***Cases*** [(b)]	***Female*** [(b)]	***Male*** [(b)]
Treatment-seeking	***No***	23,362	16,789	4,222	12,528	10,834
	Yes	48,054	14,700	25,810	32,706	15,348
	Prev. [(*)]	0.67	0.47	0.86	0.72	0.59
Treatment-receipt	***No***	7,670	4,005	2,552	4,914	2,756
	Yes	40,436	10,715	23,283	27,829	12,607
	Prev. [(*)]	0.84	0.73	0.9	0.85	0.82
Self-help	***No***	60,091	29,451	22,515	36,132	23,959
	Yes	15,231	4,317	8,519	11,587	3,644
	Prev. [(*)]	0.2	0.13	0.27	0.24	0.13
Self-medication	***No***	64,171	30,642	24,714	41,670	22,501
	Yes	10,957	3,042	6,252	5,924	5,033
	Prev. [(*)]	0.15	0.09	0.2	0.12	0.18

(*) Proportion of individuals that endorse each phenotype in (a) individuals who report on the phenotype, drawn from the full sample and (b) individuals who report on the phenotype, drawn from each strata; No = never in their lifetime; Yes = at least once in their lifetime

Table 2. Overlap between treatment seeking phenotypes

		Treatment-seeking [(i)]								
		No	***Yes***	**%**[(a)]						
Treatment-receipt [(ii)]	***No***	0	7,665	100						
	Yes	0	40,389	100	**Treatment-receipt** [(i)]					
	%[(b)]	-	84		***No***	***Yes***	**%**[(a)]			
Self-help [(ii)]	***No***	20,831	35,971	63.3	6,100	29,916	83.1			
	Yes	2,521	12,056	82.7	1,557	10,506	87.1	**Self-help** [(i)]		
	%[(b)]	10.8	25.1		20.3	26		***No***	***Yes***	**%**[(a)]
Self-medication [(ii)]	***No***	20,517	40,324	66.3	6,684	33,685	83.4	52,453	11,708	18.2
	Yes	2,772	7,603	73.3	933	6,677	87.7	7,467	3,488	31.8
	%[(b)]	11.9	15.9		12.2	16.5		12.5	23	

(a) *% of individuals who endorse phenotype (i) out of the total number of individuals who either have never endorsed (0) or have endorsed (1) phenotype (ii);* ***(b)*** *% of individuals who endorse phenotype (ii) out of the total number of individuals who either (0) have never endorsed or (1) have endorsed phenotype (i); No = never in their lifetime; Yes = at least once in their lifetime*

Heritability analyses

Our analyses indicate that treatment-seeking is modestly heritable. In the whole cohort we detect small, but significant estimates of common variant heritability for treatment-seeking (h^2_{SNP} =3.9% se=.7%),

self-medication (h^2_{SNP} =3.4% se=.7%) and self-help (h^2_{SNP} =2% se=.6%; Figure 1a). The heritability of receiving treatment (as opposed to seeking treatment but not receiving it) was smaller than our analysis was powered to detect (80% power to detect h^2_{SNP}=4.5%; 70% power to detect h^2_{SNP} =4%; GCTA power calculator: Hemani and Yang 2017).

We also estimated the heritability of all the treatment-related phenotypes in cases and controls, and in males and females separately (Figure 1a). However, in these smaller sub samples, the estimates are small and standard errors are large and overlap substantially. This could suggest that the estimates are not significantly different between strata (cases/controls; males/females). It is more likely that we are underpowered to detect subtle differences.

The lifetime prevalences of treatment-related phenotypes are difficult to estimate, so we converted estimates to the liability scale across the full range of population prevalence (Figure 1b). Heritability on the liability scale ranges from 2% to 9% for treatment-seeking, 2% to 5% for self-medication and 1% to 6% for self-help. Again, the standard errors of the heritability estimates overlap substantially when the analyses are stratified by case-control status.

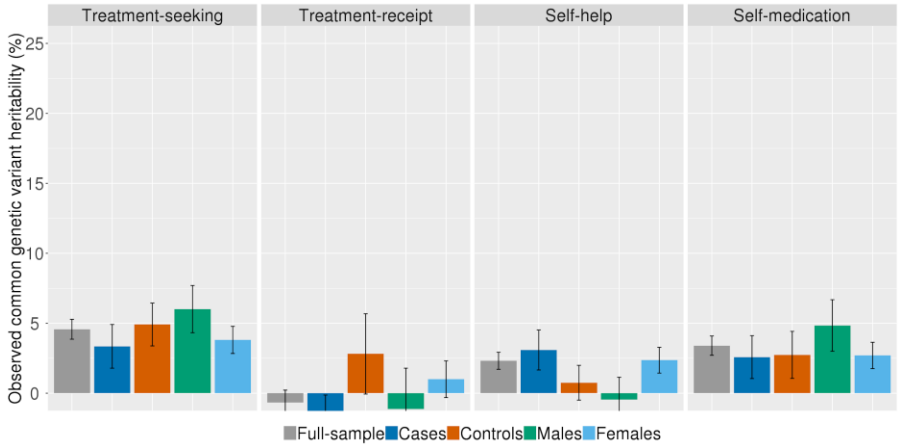
Genetic correlations

Treatment-seeking, self-help and self-medication all show modest genetic correlations with one another, that are not significant after multiple testing correction. Treatment-seeking has genetic correlations with both self-medication (r_g=.36, se=.13) and self-help (r_g=.52, se=.15). Self-medication has a genetic correlation with self-help (r_g=.65, se=.17). Treatment-seeking has significant, positive genetic correlations with anxiety disorders (Purves et al. 2017), major depression (Wray et al. 2018) and related traits (Figure 2). Self-help has positive genetic correlations with educational attainment (Lee et al. 2018), schizophrenia (Ripke et al. 2014), bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011), cross disorder psychopathology (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013), anxiety disorders (r_g~.5; Figure 2) and a negative genetic correlation with body mass index (r_g=-.24; (Yengo et al. 2018). Self-medication has significant positive genetic correlations with social deprivation (Hill et al. 2016), cannabis use (Stringer et al. 2016), schizophrenia,

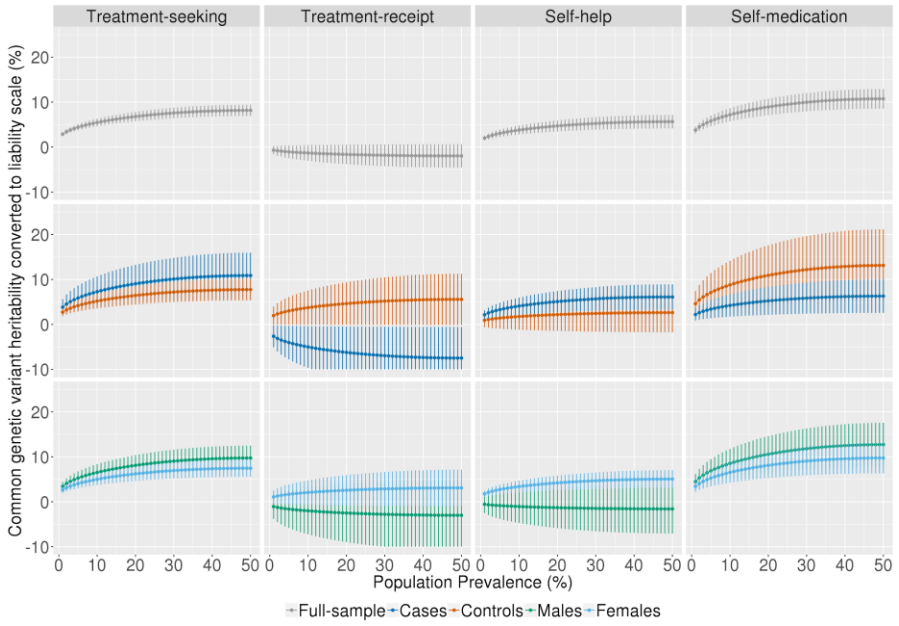
alcohol use (Schumann et al. 2016) and alcohol dependence (Walters et al. 2018) (range r_g=.26-.62; Figure 2).

Figure 1 (a) Observed common genetic variant heritability estimates of treatment-seeking phenotypes in the whole cohort, and stratified by case/control status and sex; (b) Common genetic variant heritability curves: heritability estimates of treatment-seeking phenotypes converted to the liability scale at the full range of population prevalence

(a)

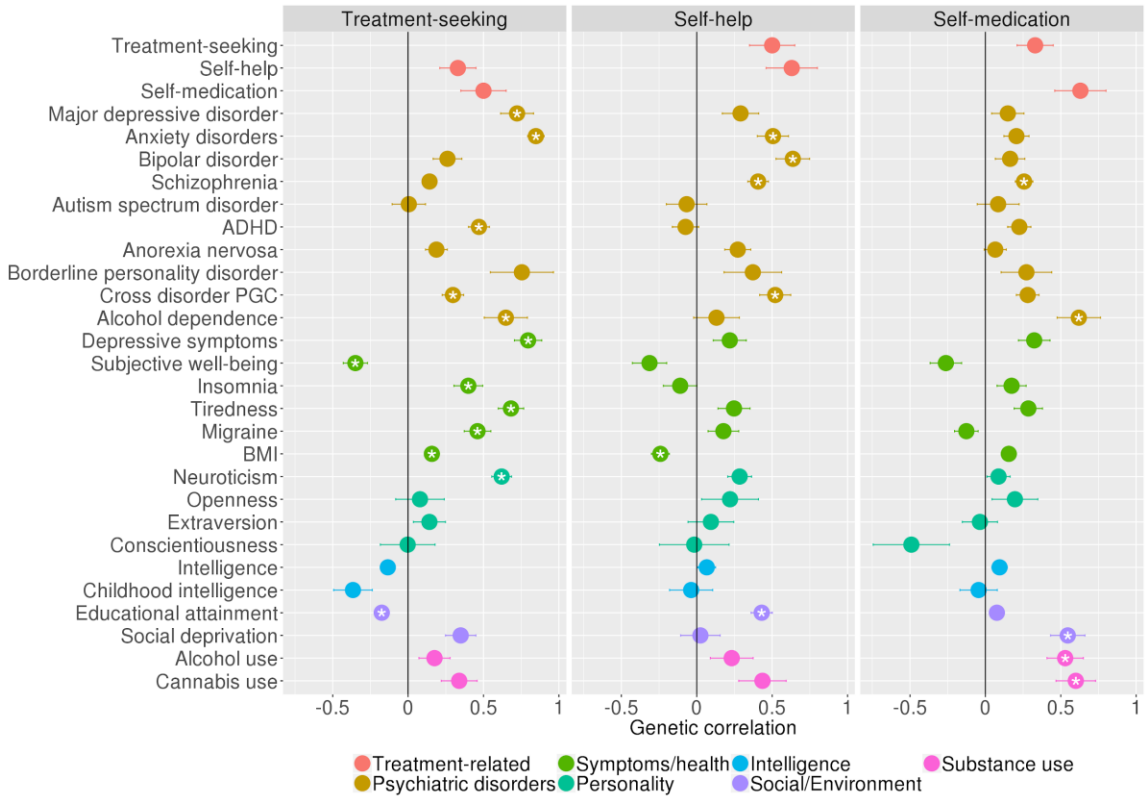


(b)



Note: error bars represent standard errors. Overlapping standard errors indicate that estimates are not significantly different between strata (tested formally via block jackknife; see supplement). Negative estimates indicate that the heritability is smaller than our analyses were powered to detect. Heritability estimates, intercept estimates and standard errors are presented in the supplement. Heritability on the liability scale peaks at 50% population prevalence. A deviation from 50% population prevalence provides the same heritability same estimate regardless of direction (+/-), i.e liability scale h^2 at a pop. prev of 20% is equal to liability scale h^2 at a pop. prev of 80%. Thus, liability scale h^2 is only plotted at 0-50% population prevalence.

Figure 2. Genetic correlations between the treatment seeking phenotypes and psychiatric, and behavioural traits



*(Note: * Bonferroni p<0.0001; error bars represent standard errors; GWAS summary statistics obtained from: major depressive disorder (Wray et al. 2018), anxiety disorders (Purves et al. 2017), bipolar disorder (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011), schizophrenia (Ripke et al. 2014), autism spectrum disorder (Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium 2017), ADHD (Demontis et al. 2018), anorexia nervosa (Bulik et al. 2017), borderline personality disorder (Witt et al. 2017), cross-disorder psychopathology (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013), alcohol dependence (Walters et al. 2018), depressive symptoms ((Okbay et al. 2016), insomnia (Hammerschlag et al. 2017), tiredness (Deary et al. 2018), migraine (Gormley et al. 2016), BMI (Yengo et al. 2018), neuroticism and subjective well-being (Okbay et al. 2016), extraversion, openness to experience, and conscientiousness (de Moor et al. 2010), intelligence (adult IQ: (Savage et al. 2018; Benyamin et al. 2014)child IQ:(Savage et al. 2018; Benyamin et al. 2014), educational attainment (Lee et al. 2018), social deprivation (Hill et al. 2016), alcohol use (Schumann et al. 2016), cannabis use ((Schumann et al. 2016; Stringer et al. 2016)**)***

We were particularly interested in understanding whether the genetic contributions to treatment-seeking differed between anxiety/depression cases and controls. Stratified analyses resulted in reduced statistical power to detect genetic correlations after multiple testing correction. Estimates were not significantly different between the strata and standard errors overlap substantially (see Supplementary Figure 5). Of note, no significant genetic correlations were observed with treatment-seeking in cases, whereas in controls, significant positive genetic correlations were observed between treatment seeking and anxiety disorders, and neuroticism. This might suggest that within controls, those with higher genetic propensity for anxiety/neuroticism were more likely to seek treatment. In contrast, for self-help significant positive genetic correlations with schizophrenia and educational attainment were observed in cases: cases who self-help have higher genetic propensity for educational attainment and schizophrenia compared to cases who do not self-help (see Supplementary Figure 5).

As a final step, we performed secondary analyses using data available from the entire UK Biobank sample, which assessed **formal** treatment-seeking. This terminology refers to when someone has specifically sought treatment (in this case for nerves, anxiety, tension or depression) from a medical professional, i.e. a GP or psychiatrist. Further details including results are presented in the supplemental material.

Discussion

To our knowledge, this is the first study to use genomic data to examine genetic influences on treatment-seeking and related phenotypes. A recent study estimated that as many as 75% of individuals suffering with symptoms of anxiety and depression, are not receiving treatment when in need, i.e. the treatment gap (Thornicroft et al. 2017). We utilised participant responses to the UK Biobank mental health questionnaire (MHQ), which assessed adults for lifetime mental health, and their responses to mental health symptoms. Responses included seeking-treatment, receiving treatment, self-sourcing a remedy or therapeutic activity, or self-medicating with alcohol and/or drugs.

Of the UK Biobank participants who completed the MHQ and who endorse at least one symptom of anxiety/depression (necessary for inclusion), the lifetime prevalence of anxiety and/or depression was 41%. More than 85% of those who met lifetime criteria for a diagnosis, sought help, and 90% of those

who sought help, received treatment. Of note, 47% of individuals who have experienced an anxiety/depression symptom seek help, even though they do not necessarily meet criteria for a clinical diagnosis. Furthermore, 73% of these individuals go on to receive treatment.

The treatment gap estimated in this sample is thus much lower than previous point prevalence estimates. Previous estimates from the UK suggest that at any one point in time, only ~30% of individuals are receiving the treatment they need (McManus et al. 2016; Thornicroft et al. 2017). There are several reasons why rates of treatment are much higher in this UK biobank sample than in previous studies. Firstly, our estimate reflects lifetime prevalence of treatment-seeking and treatment-receipt rather than the point prevalence estimates provided elsewhere (McManus et al. 2016; Thornicroft et al. 2017). Of course, individuals are more likely to have received treatment at some point in their lives than in the context of any single episode. As such, these estimates (90% lifetime prevalence of treatment-receipt; ~30% point prevalence of treatment-receipt) are not directly comparable.

The high rates of treatment-seeking and receipt in this UK Biobank study may also be related to other aspects of the study design. All participants in these analyses endorsed at least one of the four core common mental health symptom screening items, and as such are not symptom-free. Moreover, the UK Biobank sample (particularly the MHQ respondent sub-sample) has more individuals from high socioeconomic backgrounds, and with high educational attainment, than the general UK population (Davis et al. 2018). These characteristics are associated with greater access to treatment (Delgadillo et al. 2016).

Our goal was to determine whether lifetime treatment-seeking behaviour was influenced by common genetic variation, and if so, whether treatment-seeking shared genetic influences with psychiatric disorders and behavioural traits. Our analyses indicate that treatment-seeking, self-medication and self-help in response to symptoms of anxiety or depression are only modestly heritable phenotypes in these data. The phenotypes examined here are drawn from self-report data of *lifetime* experiences, thus we are unable to draw strong conclusions regarding genetic influence on treatment-seeking at a given point in time (i.e. specifically at the time of need). Future research on this topic would ideally identify groups of individuals with current symptoms including both those receiving and not receiving treatment.

This would enable a more precise estimation of the role of genetic factors with respect to accessing and receiving treatment.

We used linkage disequilibrium score regression to estimate heritability and genetic correlation because it is less computationally demanding than other methods and enables the calculation of genetic correlations with external traits (such as the psychiatric disorders and behavioural traits included herein). However, it is likely that LD score regression underestimates heritability, relative to other contemporary approaches (Evans et al. 2017; Ni et al. 2018). It is also important to note that SNP heritability estimates only consider common genetic variation, rather than the whole genome. Twin heritability estimates, which capture the proportion of variation in a trait due to all genetic influences are usually at least twice that of SNP heritability estimates (Polderman et al. 2015; Brainstorm Consortium et al. 2018). As such, our estimates are likely to represent the lower bounds of heritability for treatment-seeking and related traits.

The genetic overlap between treatment seeking and both anxiety and depression, as well as the high genetic correlations with the remaining traits, reflect a similar pattern of genetic correlations to that observed in genetic studies of depression and anxiety disorders themselves (Brainstorm Consortium et al. 2018). This suggests that the genetic influences on treatment-seeking for anxiety and depression are largely the same as those influencing the experience of these disorders. Indeed, one might expect that the primary genetic influences on treatment seeking are related to symptom severity. However, some individuals who need treatment do not seek it. Therefore, we were also interested in whether additional genetically influenced characteristics influence treatment-seeking. In order to try and examine treatment-seeking as a behaviour independent of symptom experience, we stratified our analyses by case/control status. As such, we contrasted individuals who need treatment but don't seek it, with individuals who seek treatment but don't meet criteria for a diagnosis. We found no significant differences between these two strata. Of note, by halving our sample, we lost power to detect any subtle differences.

We also examined genetic influences on self-help and self-medication. Self-help shows a similarly wide set of genetic correlations, though fewer reach statistical significance. With regard to psychiatric phenotypes, self-help is genetically correlated with anxiety disorder, bipolar disorder, schizophrenia and general psychopathology. There is also a small negative, but significant, genetic

correlation with BMI, suggesting that those with a genetic predisposition towards a lower weight are more likely to engage in self-help behaviours. This might be explained by the inclusion in the self-help category of exercise as a way to deal with symptoms. Interestingly self-help is positively genetically correlated with educational outcomes (compared to negative genetic correlations between treatment seeking and education). This genetic correlation remains significant in individuals with a diagnosis, but not in individuals without. This could suggest that genetic influences on educational achievement promote positive lifestyle habits (such as yoga or mindfulness) reducing symptoms and the need for clinical treatment. However, we cannot draw any strong conclusions from this data. Although the estimate is significant in individuals with a diagnosis, but not in individuals without, standard errors overlap substantially (Supplementary Figure 5).

Self-medication is significantly genetically correlated with schizophrenia, alcohol dependence, alcohol use and cannabis use. The strong weighting towards genetic correlations with substance use variables is to be expected, due to the phenotypic similarity. Of particular interest, self-medication has a significant genetic correlation with social deprivation (r_g=.55; se=.11). Genes influencing self-medication with drugs or alcohol thus also tend to be associated with social deprivation.

When we performed secondary analyses examining **formal** treatment-seeking (i.e. specifically seeking treatment from a GP or psychiatrist, see supplemental material) we also detected a significant genetic correlation between formal treatment-seeking and social deprivation (r_g=0.44, se=0.06; note: this genetic correlation was observed in our primary analysis, but was not significant after corrections; r_g=0.35, se=0.1). This could reflect a greater genetic vulnerability for symptoms, need for treatment and self-medication among socially deprived individuals. A recent study has shown that there is greater demand for, but poorer access to treatment in socially deprived areas, known as the ‘inverse care law’ (Saxon et al. 2007; Delgadillo et al. 2016). Public health interventions aiming to reduce rates of anxiety, depression and incidentally alcohol and drug abuse, should focus on improving the number of individuals who receive and remain in treatment for anxiety and/or depression in socially deprived areas. Further phenotypic analyses are required to disentangle social factors associated with treatment-seeking, treatment-receipt and self-medication.

In conclusion, treatment seeking behaviours are modestly heritable. Nonetheless, we were able to detect interesting genetic correlations with statistical significance, which provide some preliminary insights on the genetic architecture of these treatment related behaviours. It should be noted that when the heritability of a trait is modest, estimates of genetic correlation can be inflated. As such, these estimates should be interpreted with caution. Further work is required to unpick the specific genetic influences on treatment seeking and related phenotypes. This could be facilitated by novel genomic methods, which allow for the combined analyses of multiple traits. Given that treatment-seeking is heritable, it will be necessary for genomic studies of treatment response (i.e pharmacogenetics and therapygenetics) to account and adjust for genetic influences on treatment-seeking in order to delineate the genetic mechanisms of response. In other words, when identifying genes that influence outcomes following treatment, it will be important to take into account genetic influences on treatment seeking so that these are not incorrectly thought to influence outcome. More work is needed to work out how best to make such an adjustment.

Finally, our findings suggest that there is shared genetic risk for social deprivation with both treatment-seeking, and self-medication with drugs/alcohol. While genetics can be used to highlight behaviours and environments that share genetic risk, work investigating social, demographic or clinical barriers to treatment will be required to identify actionable predictors. Currently, whilst half of those treated recover, only ~30% of those with clinical symptoms receive treatment. As such, identifying barriers to treatment should be a public health research priority. Improving timely access to treatment will be essential to reduce the burden of untreated anxiety and depression. Future work would benefit from prospective and longitudinal study designs, collecting detailed clinical, social, demographic and genetic data. Such data could enable precision medicine initiatives to predict need-for-treatment and guide assertive outreach interventions towards those that are unlikely to seek and/or receive treatment.

References

Allen, Naomi E., Cathie Sudlow, Tim Peakman, Rory Collins, and UK Biobank. 2014. “UK Biobank Data: Come and Get It.” *Science Translational Medicine* 6 (224): 224ed4.

Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium. 2017. “Meta-Analysis of GWAS of over 16,000 Individuals with Autism Spectrum Disorder Highlights a Novel Locus at 10q24.32 and a Significant Overlap with Schizophrenia.” *Molecular Autism* 8 (1): 21.

Benyamin, B., Bst Pourcain, O. S. Davis, G. Davies, N. K. Hansell, M-J A. Brion, R. M. Kirkpatrick, et al. 2014. “Childhood Intelligence Is Heritable, Highly Polygenic and Associated with FNBP1L.” *Molecular Psychiatry* 19 (2): 253–58.

Brainstorm Consortium, Verneri Anttila, Brendan Bulik-Sullivan, Hilary K. Finucane, Raymond K. Walters, Jose Bras, Laramie Duncan, et al. 2018. “Analysis of Shared Heritability in Common Disorders of the Brain.” *Science* 360 (6395). https://doi.org/10.1126/science.aap8757.

Bulik, Cynthia, Laramie Duncan, Gerome Breen, and PGC_AN Working Group. 2017. “The PGC Gwas Meta-Analysis of Anorexia Nervosa: SNP Heritability, Genetic Correlations, And Snp Results.” *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 27 (January): S360–61.

Bulik-Sullivan, Brendan K., Po-Ru Loh, Hilary K. Finucane, Stephan Ripke, Jian Yang, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nick Patterson, Mark J. Daly, Alkes L. Price, and Benjamin M. Neale. 2015. “LD Score Regression Distinguishes Confounding from Polygenicity in Genome-Wide Association Studies.” *Nature Genetics* 47 (3): 291–95.

Bycroft, Clare, Colin Freeman, Desislava Petkova, Gavin Band, Lloyd T. Elliott, Kevin Sharp, Allan Motyer, et al. 2017. “Genome-Wide Genetic Data on ~500,000 UK Biobank Participants.” *bioRxiv*. http://www.biorxiv.org/content/early/2017/07/20/166298.

Carter, Janet D., Marie T. Crowe, Jennifer Jordan, Virginia V. W. McIntosh, Christopher Frampton, and Peter R. Joyce. 2015. “Predictors of Response to CBT and IPT for Depression; the Contribution of Therapy Process.” *Behaviour Research and Therapy* 74 (November): 72–79.

Carter, J., C. Frampton, J. McKenzie, R. Mulder, S. Luty, and P. Joyce. 2006. “Patient Predictors of Response to Interpersonal Psychotherapy and Cognitive Behaviour Therapy.” *Acta Neuropsychiatrica* 18 (6): 245–46.

Chisholm, Dan, Kim Sweeny, Peter Sheehan, Bruce Rasmussen, Filip Smit, Pim Cuijpers, and Shekhar Saxena. 2016. “Scaling-up Treatment of Depression and Anxiety: A Global Return on Investment Analysis.” *The Lancet. Psychiatry* 3 (5): 415–24.

Coleman, Jonathan R. I., Kirstin L. Purves, Katrina A. S. Davis, Christopher Rayner, Shing Wan Choi, Christopher Hübel, Héléna A. Gaspar, et al. 2018. “Genome-Wide Gene-Environment Analyses of Depression and Reported Lifetime Traumatic Experiences in UK Biobank.” *bioRxiv*. https://doi.org/10.1101/247353.

Cross-Disorder Group of the Psychiatric Genomics Consortium. 2013. “Identification of Risk Loci with

Shared Effects on Five Major Psychiatric Disorders: A Genome-Wide Analysis." *The Lancet* 381 (9875): 1371–79.

Davis, Katrina A. S., Jonathan R. I. Coleman, Mark Adams, Naomi Allen, Gerome Breen, Breda Cullen, Chris Dickens, et al. 2018. "Mental Health in UK Biobank: Development, Implementation and Results from an Online Questionnaire Completed by 157 366 Participants." *BJPsych Open* 4 (3): 83–90.

Deary, V., S. P. Hagenaars, S. E. Harris, W. D. Hill, G. Davies, D. C. M. Liewald, International Consortium for Blood Pressure GWAS, et al. 2018. "Genetic Contributions to Self-Reported Tiredness." *Molecular Psychiatry* 23 (3): 609–20.

Delgadillo, Jaime, Miqdad Asaria, Shehzad Ali, and Simon Gilbody. 2016. "On Poverty, Politics and Psychology: The Socioeconomic Gradient of Mental Healthcare Utilisation and Outcomes." *The British Journal of Psychiatry: The Journal of Mental Science* 209 (5): 429–30.

Demontis, Ditte, Raymond K. Walters, Joanna Martin, Manuel Mattheisen, Thomas D. Als, Esben Agerbo, Gísli Baldursson, et al. 2018. "Discovery of the First Genome-Wide Significant Risk Loci for Attention Deficit/hyperactivity Disorder." *Nature Genetics*, November. https://doi.org/10.1038/s41588-018-0269-7.

Evans, Luke, Rasool Tahmasbi, Scott Vrieze, Goncalo Abecasis, Sayantan Das, Doug Bjelland, Teresa deCandia, et al. 2017. "Comparison of Methods That Use Whole Genome Data to Estimate the Heritability and Genetic Architecture of Complex Traits." *bioRxiv*. https://doi.org/10.1101/115527.

Gage, Suzanne H., George Davey Smith, Jennifer J. Ware, Jonathan Flint, Marcus R. Munafò, and R. Koifman. 2016. "G = E: What GWAS Can Tell Us about the Environment." Edited by Greg Gibson. *PLoS Genetics* 12 (2): e1005765.

Gormley, Padhraig, Verneri Anttila, Bendik S. Winsvold, Priit Palta, Tonu Esko, Tune H. Pers, Kai-How Farh, et al. 2016. "Meta-Analysis of 375,000 Individuals Identifies 38 Susceptibility Loci for Migraine." *Nature Genetics* 48 (8): 856–66.

Hammerschlag, Anke R., Sven Stringer, Christiaan A. de Leeuw, Suzanne Sniekers, Erdogan Taskesen, Kyoko Watanabe, Tessa F. Blanken, et al. 2017. "Genome-Wide Association Analysis of Insomnia Complaints Identifies Risk Genes and Genetic Overlap with Psychiatric and Metabolic Traits." *Nature Genetics* 49 (11): 1584–92.

Hemani, G., and J. Yang. 2017. "Gcta-Greml Power Calculator."

Henderson, Claire, Sara Evans-Lacko, and Graham Thornicroft. 2013. "Mental Illness Stigma, Help Seeking, and Public Health Programs." *American Journal of Public Health* 103 (5): 777–80.

Hill, W. David, Saskia P. Hagenaars, Riccardo E. Marioni, Sarah E. Harris, David C. M. Liewald, Gail Davies, Aysu Okbay, Andrew M. McIntosh, Catharine R. Gale, and Ian J. Deary. 2016. "Molecular Genetic Contributions to Social Deprivation and Household Income in UK Biobank." *Current Biology: CB* 26 (22): 3083–89.

Kendler, Kenneth S., and Jessica Baker. 2007. "Genetic Influences on Measures of the Environment: A Systematic Review." *Psychological Medicine* 37 (05): 615.

Kohn, Robert, Shekhar Saxena, Itzhak Levav, and Benedetto Saraceno. 2004. “The Treatment Gap in Mental Health Care.” *Bulletin of the World Health Organization* 82 (11): 858–66.

Lambert, Michael J., and Dean E. Barley. 2001. “Research Summary on the Therapeutic Relationship and Psychotherapy Outcome.” *Psychotherapy: Theory, Research, Practice, Training* 38 (4): 357–61.

Lee, James J., Robbee Wedow, Aysu Okbay, Edward Kong, Omeed Maghzian, Meghan Zacher, Tuan Anh Nguyen-Viet, et al. 2018. “Gene Discovery and Polygenic Prediction from a Genome-Wide Association Study of Educational Attainment in 1.1 Million Individuals.” *Nature Genetics* 50 (8): 1112–21.

McCarthy, Shane, Sayantan Das, Warren Kretzschmar, Olivier Delaneau, Andrew R. Wood, Alexander Teumer, Hyun Min Kang, et al. 2016. “A Reference Panel of 64,976 Haplotypes for Genotype Imputation.” *Nature Genetics* 48 (10): 1279–83.

McManus, Sally, Paul Bebbington, Louis Appleby, Philip Asherson, Abdolreza Ashtarikiani, Camille Aznar, Sally Bridges, et al. 2016. “Mental Health and Well-Being in England: Adult Psychiatric Morbidity Survey 2014.” *NHS Digital*.

Moor, M. H. M. de, P. T. Costa, A. Terracciano, R. F. Krueger, E. J. C. de Geus, T. Toshiko, B. W. J. H. Penninx, et al. 2010. “Meta-Analysis of Genome-Wide Association Studies for Personality.” *Molecular Psychiatry* 17 (December): 337.

Ni, Guiyan, Gerhard Moser, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Naomi R. Wray, and S. Hong Lee. 2018. “Estimation of Genetic Correlation via Linkage Disequilibrium Score Regression and Genomic Restricted Maximum Likelihood.” *American Journal of Human Genetics* 102 (6): 1185–94.

Okbay, Aysu, Bart M. L. Baselmans, Jan-Emmanuel De Neve, Patrick Turley, Michel G. Nivard, Mark Alan Fontana, S. Fleur W. Meddens, et al. 2016. “Genetic Variants Associated with Subjective Well-Being, Depressive Symptoms, and Neuroticism Identified through Genome-Wide Analyses.” *Nature Genetics* 48 (6): 624–33.

Ownby, Raymond L., Amarilis Acevedo, Robin J. Jacobs, Joshua Caballero, and Drenna Waldrop-Valverde. 2014. “Negative and Positive Beliefs Related to Mood and Health.” *American Journal of Health Behavior* 38 (4): 586–97.

Polderman, Tinca J. C., Beben Benyamin, Christiaan A. de Leeuw, Patrick F. Sullivan, Arjen van Bochoven, Peter M. Visscher, and Danielle Posthuma. 2015. “Meta-Analysis of the Heritability of Human Traits Based on Fifty Years of Twin Studies.” *Nature Genetics* 47 (7): 702–9.

Psychiatric GWAS Consortium Bipolar Disorder Working Group. 2011. “Large-Scale Genome-Wide Association Analysis of Bipolar Disorder Identifies a New Susceptibility Locus near ODZ4.” *Nature Genetics* 43 (10): 977–83.

Purves, Kirstin, Jonathan R. I. Coleman, Chris Rayner, Jack M. Hettema, Jurgen Deckert, Andrew M. McIntosh, Kristin Nicodemus, Gerome Breen, and Thalia C. Eley. 2017. “The Common Genetic Architecture of Anxiety Disorders.” *BioRxiv*. https://doi.org/10.1101/203844.

Ripke, Stephan, Benjamin M. Neale, Aiden Corvin, James T. R. Walters, Kai-How Farh, Peter A. Holmans, Phil Lee, et al. 2014. “Biological Insights from 108 Schizophrenia-Associated Genetic Loci.” *Nature* 511 (7510): 421–27.

Savage, Jeanne E., Philip R. Jansen, Sven Stringer, Kyoko Watanabe, Julien Bryois, Christiaan A. de Leeuw, Mats Nagel, et al. 2018. “Genome-Wide Association Meta-Analysis in 269,867 Individuals Identifies New Genetic and Functional Links to Intelligence.” *Nature Genetics*, June. https://doi.org/10.1038/s41588-018-0152-6.

Saxon, David, Gearoid Fitzgerald, Simon Houghton, Francesca Lemme, Carol Saul, Sharon Warden, and Tom Ricketts. 2007. “Psychotherapy Provision, Socioeconomic Deprivation, and the Inverse Care Law.” *Psychotherapy Research: Journal of the Society for Psychotherapy Research* 17 (5): 515–21.

Schumann, Gunter, Chunyu Liu, Paul O’Reilly, He Gao, Parkyong Song, Bing Xu, Barbara Ruggeri, et al. 2016. “KLB Is Associated with Alcohol Drinking, and Its Gene Product β-Klotho Is Necessary for FGF21 Regulation of Alcohol Preference.” *Proceedings of the National Academy of Sciences of the United States of America* 113 (50): 14372–77.

Spinath, Frank M., and Wiebke Bleidorn. 2017. “The New Look of Behavioral Genetics in Social Inequality: Gene-Environment Interplay and Life Chances.” *Journal of Personality* 85 (1): 5–9.

Stringer, S., C. C. Minică, K. J. H. Verweij, H. Mbarek, M. Bernard, J. Derringer, K. R. van Eijk, et al. 2016. “Genome-Wide Association Study of Lifetime Cannabis Use Based on a Large Meta-Analytic Sample of 32 330 Subjects from the International Cannabis Consortium.” *Translational Psychiatry* 6 (March): e769.

Thapar, A., G. Harold, and P. McGuffin. 1998. “Life Events and Depressive Symptoms in Childhood--Shared Genes or Shared Adversity? A Research Note.” *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 39 (8): 1153–58.

Thornicroft, Graham. 2008. “Stigma and Discrimination Limit Access to Mental Health Care.” *Epidemiologia E Psichiatria Sociale* 17 (1): 14–19.

Thornicroft, Graham, Somnath Chatterji, Sara Evans-Lacko, Michael Gruber, Nancy Sampson, Sergio Aguilar-Gaxiola, Ali Al-Hamzawi, et al. 2017. “Undertreatment of People with Major Depressive Disorder in 21 Countries.” *The British Journal of Psychiatry: The Journal of Mental Science* 210 (2): 119–24.

Visscher, Peter M., William G. Hill, and Naomi R. Wray. 2008. “Heritability in the Genomics Era--Concepts and Misconceptions.” *Nature Reviews. Genetics* 9 (4): 255–66.

Walters, Raymond K., Mark J. Adams, Amy E. Adkins, Fazil Aliev, Silviu-Alin Bacanu, Anthony Batzler, Sarah Bertelsen, et al. 2018. “Trans-Ancestral GWAS of Alcohol Dependence Reveals Common Genetic Underpinnings with Psychiatric Disorders.” *bioRxiv*. https://doi.org/10.1101/257311.

Witt, S. H., F. Streit, M. Jungkunz, J. Frank, S. Awasthi, C. S. Reinbold, J. Treutlein, et al. 2017. “Genome-Wide Association Study of Borderline Personality Disorder Reveals Genetic Overlap with Bipolar Disorder, Major Depression and Schizophrenia.” *Translational Psychiatry* 7 (6): e1155.

Wray, Naomi R., Stephan Ripke, Manuel Mattheisen, Maciej Trzaskowski, Enda M. Byrne, Abdel Abdellaoui, Mark J. Adams, et al. 2018. “Genome-Wide Association Analyses Identify 44 Risk Variants and Refine the Genetic Architecture of Major Depression.” *Nature Genetics* 50 (5): 668–81.

Yengo, Loic, Julia Sidorenko, Kathryn E. Kemper, Zhili Zheng, Andrew R. Wood, Michael N. Weedon, Timothy M. Frayling, et al. 2018. “Meta-Analysis of Genome-Wide Association Studies for Height and Body Mass Index in ~700,000 Individuals of European Ancestry.” *bioRxiv*. https://doi.org/10.1101/274654.